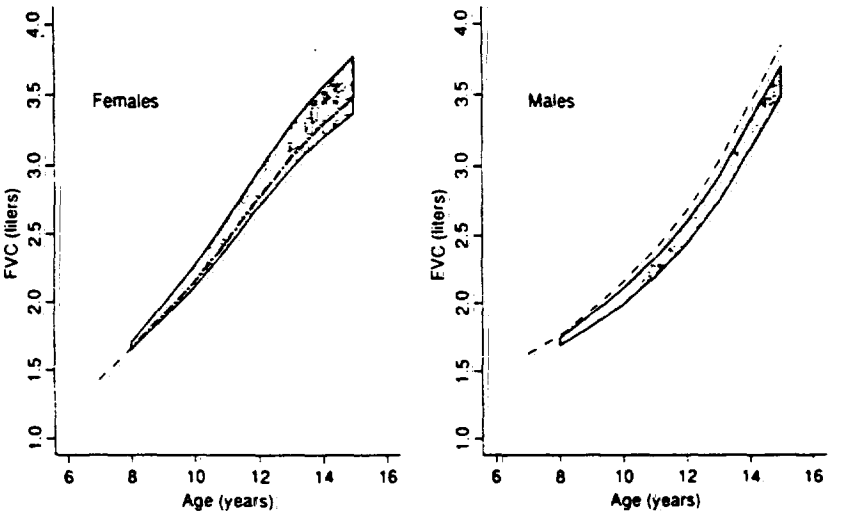

Fig. 1. Projected FVC for female and male subjects from age 8 to age 15. The shaded area represents confidence limits for the projected FVC of normal subjects. The broken line is the projected FVC for subjects with active asthma beginning at age 7.

for males and the FEV and FEF_{25-75} results for females outside the 95% confidence limits for normal change in growth of lung function in this random population sample.

Few longitudinal studies of the effect of asthma on lung growth exist. The largest prospective study of the effect of asthma on lung growth in children was performed by Williams and McNicol in Australia (1–4, 21). A total of 378 asthmatic and 105 control subjects were initially seen in 1964, again in 1967, and in 1981, 14 yr later; 331 (88%) of the asthmatic and 72 (69%) of the control subjects were seen in the second follow-up. Subjects with current symptoms were likely to have reduced levels of both FEV_1 and FEF_{25-75}. Martin and colleagues, analyzing a subgroup of this cohort, reported that those subjects with asthma that persisted from childhood were more likely to have both an elevated vital capacity and total lung capacity than those with intermittent symptoms (2). They also noted that girls did less well during adolescence than boys such that the gender ratio for severe disease was equal (4). Thus, their results are consistent with our observations.

The crude analysis comparing average percentage of predicted lung function in ever-asthmatic subjects (table 2) provides, for the most part, slightly larger values for the differences between groups than the longitudinal modeling analyses, which consider active and inactive asthma (table 4). This may be because the longitudinal modeling explicitly controls for baseline or initial lung function and growth, whereas the crude analysis does not. The congruence between the crude and the multivariate modeling confirms that these results are not an artefact of the modeling process.

Asthma is more prevalent in boys than girls in both our cohort and the U.S. population (22). Lack of sex stratification, as in the study of Martin (2), would result in a balancing out of the male-female differences weighted toward the male (more prevalent effect). This tends to confirm the common clinical dictum from early investigators that childhood asthma has a relatively benign effect on lung function, particularly in boys (23). Our results for females suggest that this is not the case. The estimated deficit in FEV_1 for a female child with active asthma for 8 yr beginning at age 7 is 7%. This effect is substantially greater than the effect of passive smoking previously observed in this cohort (8) and places this female child below the 95% confidence limits for normal growth in this population. This degree of decrement in FEV_1 may have important implications for the development of chronic lung disease in adulthood. The finding that active wheeze symptoms (active asthma, table 4) were necessary for female asthmatic subjects to experience a reduction in lung function is consistent with the concept that active airway inflammation is responsible for the reduced level of pulmonary function and provides a useful clinical marker for disease severity to assist clinicians.

In addition to reduced change in FEV_1 and FEF_{25-75}, female asthmatic subjects were more frequently hospitalized than the males (table 3). The association of hospitalization with asthma in female children is all the more striking given that, in this and other population studies of children, asthma was more common in males (24, 25). This formulation is also consistent with epidemiologic data from other population-based studies suggesting more severe asthma in female adults (25–27).

Mead used the term "dysanapsis" to indicate nonisotropic (nonproportionately equal) growth of airways and lung parenchyma resulting in either a lung that is too large or airways that are too small, or both (28). To the extent that the FEF_{25-75} reflects airways size and the FVC represents lung size, our data sup-

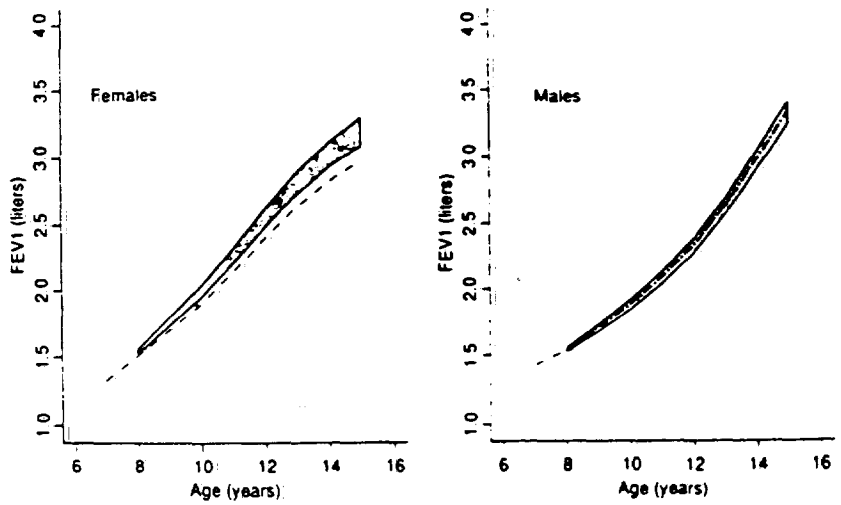

Fig. 2. Projected FEV_1 for female and male subjects from age 8 to age 15. The shaded area represents confidence limits for the projected FEV_1 of normal subjects. The broken line is the projected FEV_1 for subjects with active asthma beginning at age 7.

dependent variables, active and inactive asthma, with appropriate adjustment for the longitudinal structure of the data, including baseline differences in lung function, a first-order autoregressive model was used. Adjustment for height and growth velocity were accomplished by including height and change in height at each visit as independent variables in the regression model. Interaction terms between sex and active and inactive asthma were used to assess sex-specific effects. A random-effects approach was used to adjust for the residual correlation among siblings included in the same analysis.

The final models for all three lung function measures included previous lung function, sex, height, change in height, age, and maternal and personal smoking as independent variables. For FEV_1 and FVC, sex-height and sex-age interactions were included because preliminary fits of the model showed those interactions to be statistically significant. Maternal smoking was included for FEV_1 and FEF_{25-75}. A sex-growth interaction was included in the final model for FEF_{25-75}, and a sex-previous lung function interaction was included for FVC.

The sex-specific effects of active and inactive asthma, expressed as a percentage of the expected change in pulmonary function/year under the autoregressive model for children without asthma, holding growth and pulmonary function in the preceding year constant, are shown in table 4. The effect of active asthma on FVC was positive and statistically significant for males after adjustment for all other covariates in the model. Active asthma was not a significant predictor of change in FEV_1 for males. In contrast, for females the effect of active asthma was negative and statistically significant for change in FEV_1 but not for change in FVC. For change in FEF_{25-75}, the effect of active asthma was negative and statistically significant for both males and females. Inactive asthma was not a significant predictor for change in any measure of pulmonary function for either gender. The male-female difference column of table 4 provides a p value for the statistical significance of the difference between the effects of asthma in males and females. Overall, the findings from the autoregressive models confirm the pattern observed in the preliminary percentage of predicted analyses.

Substantial agreement is seen between the first- and second-order autoregressive models for the effect of active asthma (table 5). Examples of the sex-specific effects of asthma on lung function development implied by the final models for FVC and FEV_1 are provided graphically in figures 1 and 2. Each figure shows the projected mean pulmonary function for ages 8 through 15 for children of the same sex who begin at age 7 with the same initial level of lung function and height and experience the same growth in height at subsequent ages. The initial height and lung functions are taken from the medians in the population, as are the heights at each age. Projections for FVC are shown in figure 1, and projections for FEV_1 are shown in figure 2. From the data used to generate figure 2, we calculate that a female with a continuing history of asthma achieves only 95% of the FEV_1 by age 15.

It is important to note that age of onset of asthma is implicitly included in the autoregressive model. This is because effects persist over time in the model, with the result that older ages of onset result in smaller net effects on lung function at later ages.

TABLE 4

SEX-SPECIFIC EFFECTS OF ASTHMA ON CHANGE IN PULMONARY FUNCTION (FVC, FEV_1, FEF_{25-75}) AS ESTIMATED FROM AUTOREGRESSIVE MODELS*

	Male		Female		Male-Female	
	Effect (%)	p Value	Effect (%)	p Value	Difference	p Value
FVC						
Active asthma	2.45	0.002	−0.76	0.451	3.21	0.012
Inactive asthma	0.70	0.308	−1.05	0.437	1.75	0.246
FEV_1						
Active asthma	0.10	0.896	−2.12	0.034	2.22	0.077
Inactive asthma	0.13	0.846	−1.87	0.177	2.00	0.191
FEF_{25-75}						
Active asthma	−4.18	0.003	−5.75	0.002	1.57	0.482
Inactive asthma	−0.54	0.666	−2.88	0.255	2.34	0.669

* See text for variables included in the models. The mean effect of asthma (active and inactive) expressed as a percentage of the expected in pulmonary function for children without asthma, holding constant growth and pulmonary function in the preceding year. Refer to the text and figures 1 and 2 for assessing the cumulative effects over several years.

TABLE 5

COMPARISON OF ESTIMATES FOR THE EFFECT OF ACTIVE ASTHMA FROM FIRST- AND SECOND-ORDER AUTOREGRESSIVE MODELS

		Males		Females	
Pulmonary Function	Model	Estimate (% effect)	p Value	Estimate (% effect)	p Value
FVC	First order	2.45	0.002	−0.76	0.451
	Second order	2.68	0.001	−0.55	0.618
FEV_1	First order	0.10	0.896	−2.12	0.034
	Second order	0.55	0.497	−1.73	0.109
FEF_{25-75}	First order	−4.18	0.003	−5.75	0.002
	Second order	−2.29	0.109	−2.78	0.150

Discussion

Because of the potential importance of maximally attained level of FEV_1 as an indicator of future risk of chronic obstructive lung disease (20), the most important finding of this investigation is a deficit in change in FEV_1 for girls with a doctor's diagnosis of asthma and active wheezing symptoms. This deficit was less significant in female subjects with a past diagnosis of asthma but no active wheeze symptoms. The link between active asthma and lung function is less clear in male children. Males with active asthma had a greater change in forced vital capacity. However, both males and females with active asthma had a reduced change in FEF_{25-75}. It should be stressed that these children are a random population sample of the East Boston community. The initially normal level of pulmonary function (table 3) is consistent with this. However, the observed effect should not be construed as not clinically or biologically significant. The deficit in growth in these mildly asthmatic subjects would place the FVC and FEF_{25-75} results

port the hypothesis that dysanapsis characterizes children with asthma. In a prior investigation of 291 children from this cohort with eucapneic hyperpnea using subfreezing air as a test of bronchial responsiveness, we demonstrated that children with a decreased FEF_{25-75}/FVC ratio were more likely to respond to bronchial challenge (29). In asthmatic males, dysanapsis may be attributable in part to an increased FVC. Thus, our results are consistent with the hypothesis that mechanical factors (e.g., dysanapsis) rather than simply airway inflammation are important in determining lung function in asthmatic males. Thus as lungs and airways grow, wheezing on a mechanical basis (dysanapsis) may be less common. The relationship between dysanapsis and airway responsiveness is unclear, however, and requires further investigation.

Greaves and Colebatch (30) suggested a complementary hypothesis based on a study of 18 asthmatic subjects. Of the subjects 10 developed asthma in childhood (all were males) and 8 developed asthma after age 18 (5 males and 3 females). The male childhood asthmatic subjects had an increased total lung capacity (TLC); adult-onset asthmatic subjects had a normal TLC. Analysis of pressure-volume curves revealed the male childhood asthmatic patients to have lungs of greater distensibility but adult-onset asthmatic patients had lungs of normal distensibility. Under their hypothesis episodes of bronchospasm postnatally could influence the growth patterns in childhood asthma. This hypothesis also requires further evaluation.

Certain aspects of our study design and population must be noted. First, subjects initially were aged 5 to 9 at study onset and over half of our asthma subjects were diagnosed before study onset. As Martinez and coworkers noted, however, abnormal lung function may antedate and predict subjects at risk of wheezing symptoms (31). Without information on the pulmonary function of the cohort from birth, it is difficult to be conclusive about whether our observed differences in patterns of lung growth for both male and female asthmatic subjects are cause or consequence of a diagnosis of asthma, or both. Although male subjects with active asthma at entry had significantly lower FEF_{25-75} and female subjects with active asthma at entry had significantly lower FEV_1 (table 2), initial lung function was controlled for in our regression analysis and thus differences in this factor are unlikely to explain our results. In the longitudinal results of Sherrill and coworkers (32). Despite the limitations in causal interpretation, the quantitative nature of our results and the described patterns of change in pulmonary function are of value to clinicians and investigators interested in asthma.

It is unlikely that maternal and personal smoking account for the different effects of asthma on change in lung function in males and females observed in our study. Males and females with asthma did not differ in percentage of smoking mothers from children without asthma. Asthmatic children were more likely to report personally ever smoking than children without asthma, but significantly so only for females. In addition, the effect of these variables was adjusted for in the analysis. Finally, male and female asthmatic subjects did not differ from their nonasthmatic same-sex counterparts in terms of amount and duration of personal cigarette smoking.

A self-report of a doctor's diagnosis of asthma is a standard definition for asthma used in respiratory epidemiology in the United States. It is based on a standardized questionnaire (33). This definition has been used by the National Center for Health Statistics and other government agencies in surveys of the U.S. population. Indeed, our asthma prevalence figures are comparable to national data (12). Thus, our definition is standard in epidemiology and is generalizable to other U.S. populations.

Diagnostic bias inherent in a doctor's diagnosis of asthma is less of a problem in children than in adults (34). However, it is important to consider misclassification of disease on our results. There is a large body of data in both our own (11, 14) and other populations (35, 36) that suggests that physicians tend to underdiagnosis asthma. To the extent that this occurred in our study, the estimates of the effect of asthma on lung function are likely to be conservative.

Current concepts of asthma as a disease incorporate the notion of bronchial hyperresponsiveness (37). As alluded to in Methods, we performed a cross-sectional study to examine the prevalence of bronchial hyperresponsiveness to cold air in a random subsample of this cohort (14). In addition, results similar to those presented here were obtained when we examined airway responsiveness in this population (38). In this investigation, 11 of 12 asthmatic subjects with any wheezing in the current study year had increased bronchial responsiveness using a cutoff value for cold air challenge of a FEV/FVC. The one active asthmatic subject who did not meet this definition had a borderline (8%) decrease. No inactive asthmatic subjects had a positive cold air challenge test (14). These data tend to give credibility to our definition of asthma and to link a report of active asthma in this investigation with increased levels of bronchial responsiveness.

Simple differences in the prevalence of airway responsiveness and allergy (as manifested by skin test reactivity) also cannot explain our results. Increased airway responsiveness in populations tends to parallel the prevalence of asthma and hence is more common in males, especially at younger ages (39, 40). In children and young adults (aged 5 to 24) in our population, the prevalence of increased airway responsiveness was similar in males and females (14). Males in this and other populations are more likely to manifest allergy as measured by skin test reactivity (22, 26, 41). It is also unlikely that ethnic or socioeconomic differences between children in this cohort can explain our results, since the cohort is all white, predominantly Italian, and socioeconomically homogeneous. In addition, subjects come from a geographically defined area of the city of Boston, making differential effects of other factors, such as air pollution, unlikely. A number of other variables differ between males and females, such as height, change in height (growth), and muscle strength. Although these factors may be expected to contribute to the observed effects, height and growth were both accounted for in the analysis.

Prior analyses in this population demonstrated the importance of acute lower respiratory illness (LRI) as a predictor of the occurrence of asthma (41, 42) and as a predictor of reduced level of FEV_1 and FEF_{25-75} and of longitudinal change in FEV_1 and FEF_{25-75} (43). We directly assessed the role of retrospectively collected respiratory illness data using the illness before age 2 variable and found that this variable was not a significant predictor of longitudinal change in pulmonary function after inclusion of asthma in the model. These results are consistent with the results of Gold and coworkers (43). Whether these results are a function of recall bias, a strong causal relationship between LRI and asthma as suggested by Sherman and colleagues (42), or other factors is unclear. The role of prospectively collected LRI data on asthma and lung function has been reported previously (43). However, definitive assessment of the relationship

coefficients, subtracting 1, and multiplying the result by 100.

For the models shown in table 4, we estimated residual correlations between the logarithms of lung functions for siblings seen in the same year as 0.35 for FVC, 0.25 for FEV_1, and 0.19 for FEF_{25-75}. Although these correlations are significant and were taken into account in the final models, we found the effect of ignoring the familial clustering to be minor on the estimates of other model parameters.

Results

A total of 602 subjects initially between 5 and 9 yr of age contributed data to the analysis over the 13-yr period. These 602 subjects included 346 index subjects and 256 siblings from 334 families. An additional 193 children in this age range were initially seen in Year 1 but contributed no data to the analyses. They represented siblings of the index subjects who were not seen in Years 2 and 3 of follow-up and a small number of index subjects with missing data. The included and excluded subjects are compared with respect to their baseline characteristics in table 1. No significant differences are apparent. Included subjects were on average 6.9 yr of age at study onset, were overwhelmingly nonsmokers, and had normal pulmonary function in the initial survey.

At baseline male active asthmatic subjects had a significantly lower FEF_{25-75} than male nonasthmatic subjects, and female active asthmatic subjects had a significantly lower FEV_1 compared to female nonasthmatic subjects (table 2). A preliminary analysis was performed to examine the average percentage of predicted pulmonary function at baseline and over the 13-yr period for asthmatic and nonasthmatic subjects stratified by gender (table 2). When compared with nonasthmatic males, ever-asthmatic males had a 3% higher FVC, a 3% lower FEV_1, and an 11% lower FEF_{25-75}. Ever-asthmatic females when compared to nonasthmatic females, however, had no difference in average percentage of predicted FVC but a 9% reduction in percentage of predicted FEV_1 and an 18% decrease in percentage of predicted FEF_{25-75}.

Male and female ever-asthmatic subjects were similar with regard to a number of clinical characteristics (table 3). Females, however, were significantly more likely than males to have been hospitalized for asthma.

Male ever-asthmatic subjects did not differ from nonasthmatic males in the percentage of personal ever-smokers (5 of 42, 12%, versus 23 of 277, 8%; p = 0.556), lifetime number of cigarettes smoked (3.45 versus 3.45 pack-years; p = NS, not significant), or average number of years smoking (2.98 versus 2.91, p = 0.794). The data for females are suggestive of a difference between ever-asthmatic and nonasthmatic subjects in the percentage of personal ever-smokers (9 of 23, 39%, versus 54 of 260, 21%; p = 0.063) and the average lifetime number of years smoking (2.35 versus 2.98, p = 0.062) but not in the average number of cigarettes smoked (3.20 versus 3.46 pack-years; p = 0.555).

To evaluate the effect of the time-

TABLE 1

COMPARABILITY OF SUBJECTS INCLUDED AND EXCLUDED FROM ANALYSIS FOR SELECTED CHARACTERISTICS IN THE ENTRY YEAR

	Included	Excluded	p Value*
Numbers	602	193	–
Age (x ± SD), yr	6.9 ± 1.3	7.0 ± 1.3	0.407
Height, (x ± SD), cm	122.4 ± 9.4	121.9 ± 10.4	0.646
FEV_1 (x ± SD), L	1.15 ± 0.19	1.14 ± 0.21	0.571
Asthma, wheeze, n (%)†	30 (5.2)	11 (6.0)	0.327
Mother's smoking, n (%)‡	191 (26.9)	57 (33.5)	0.532
Sex, male, n (%)	303 (52.5)	99 (51.3)	0.411
Personal smoking, nonsmokers, n (%)§	523 (97.8)	135 (98.5)	0.798

* Two-sided p value for two-sample *t* tests or chi-squared tests

† Two asthmatic subjects missing Year 1 data

‡ There were 75 mothers missing smoking information in Year 1, 52 not in the model for males and 22 not in the model for females

§ There were 98 children missing personal smoking information in Year 1, 42 from the included group and 56 from the excluded group

TABLE 2

AVERAGE PERCENTAGE PREDICTED VALUES FOR PULMONARY FUNCTION AT ENTRY AND OVER 13 YR OF OBSERVATION FOR ASTHMATIC AND NONASTHMATIC SUBJECTS BY SEX

	FVC		FEV_1		FEF_{25-75}	
	Mean ± SD	p Value	Mean ± SD	p Value	Mean ± SD	p Value
Males						
At entry						
No asthma	101 ± 15	0.734	105 ± 16	0.675	88 ± 20	0.037
Active asthma	102 ± 18		103 ± 22		76 ± 25	
13-yr average						
No asthma	100 ± 12	0.130	103 ± 12	0.267	92 ± 18	0.003
Ever asthma	103 ± 11		100 ± 13		80 ± 22	
Females						
At entry						
No asthma	108 ± 14	0.529	116 ± 16	0.038	95 ± 21	0.072
Active asthma	104 ± 17		102 ± 16		73 ± 30	
13-yr average						
No asthma	110 ± 13	0.536	113 ± 12	0.012	100 ± 19	0.003
Ever asthma	108 ± 13		104 ± 16		82 ± 26	

* p Value for difference

TABLE 3

CHARACTERISTICS OF ASTHMATIC SUBJECTS INCLUDED IN THE ANALYSES

	Male, n = 42		Female, n = 23		
	Mean	SD	Mean	SD	p Value
Age asthma began	7.29 ± 4.66		8.61 ± 5.39		0.327
Years of asthma symptoms	3.07 ± 2.31		3.22 ± 2.02		0.793
Years of asthma medication	1.67 ± 1.99		2.26 ± 2.14		0.279
Illness before age 2*	14/42 (33%)		7/22 (32%)		0.762
Ever hospitalized for asthma	1/42 (2%)		4/23 (6%)		0.049†

* One subject missing information on illness before age 2

† By Fisher's exact test

rate questionnaires were used for subjects under 10 yr of age and for subjects 10 yr or older. A common questionnaire was used for all subjects in the third through thirteenth follow-up examinations. The questions relating to chronic respiratory symptoms were those proposed by the Division of Lung Diseases, National Heart Lung and Blood Institute for epidemiology studies (12, 13). For children aged 10 or younger, the parents answered all questions except those pertaining to the child's own smoking history; all other children answered all questions themselves.

Asthma was defined as an affirmative answer to the question, "Has a doctor ever told you that you (your child) have (has) asthma?" Any wheeze was defined as wheezing with colds or occasionally, apart from colds, or on most days and nights. For the purpose of the present analysis three different definitions of asthma were used. Subjects were defined as ever-asthma if they ever responded affirmatively to the question. All other subjects were defined as never-asthmatic. This definition disregarded disease activity and was used for the analyses presented in tables 2 and 3. In the longitudinal analyses, active asthma was considered present if a subject responded affirmatively to the ever-asthma question and had any wheezing symptoms in that study year. Subjects with a past history of asthma but who denied wheezing during the previous year were considered to have inactive asthma in that study year. This definition of active asthma was chosen because it has a high correlation with an objective test of airways responsiveness in a cross-sectional study of a representative sample of this population (14). An additional benefit of the active and inactive definitions is that the true natural history of the disease is being modeled (subjects can have active disease in one year, inactive disease the next and active disease the third, and these relationships are captured in the model).

Hospitalization and medication use were assessed by self-report of hospitalization or medication use in each survey year. Respiratory illness before age 2 was defined as parental report of a doctor's diagnosis of pneumonia, bronchitis, croup, or bronchiolitis before age 2.

Definitions of Cigarette Smoking

A mother was considered a current smoker if she had been smoking within 1 month before the time of interview for the initial examination or for the entire year before and including the time of interview for the follow-up examinations. Exsmokers were defined as those who had smoked more than 20 packs in their lifetime or more than one cigarette per day but had stopped smoking more than 1 month before the interview. For the purpose of the analysis, children with never and exsmoking mothers were compared with children with currently smoking mothers.

The child's smoking history was obtained directly from all children during pulmonary function testing, a time when parents were not present. A child was considered a current smoker if he or she smoked at least one cigarette per day within 1 month of the interview. For the purposes of this analysis, never-smokers and exsmokers were compared with current smokers.

Spirometry

Forced vital capacity (FVC) maneuvers were performed with the subjects seated without nose clips using an 8-L, water-filled portable spirometer (Survey spirometer; Warren E. Collins, Inc., Braintree, MA). Tests were performed by one of two of the same technicians (one technician performed > 90% of the tests) throughout the entire study. A test was considered acceptable if the technician assessed that a maximum effort had occurred in the face of no other technical problems (e.g., mouth leak) and all criteria for an acceptable timed forced expiratory volume (12) were met. Subjects aged 10 yr or less were encouraged to blow for at least 4 s and those over 10 yr were encouraged to blow for at least 6 s. Five acceptable tracings with vital capacities within 5% of the maximum were sought; up to eight attempts were permitted.

All tracings were hand measured by the same technician for the first nine surveys and by a second technician for the last four surveys. The second technician was standardized to the first technician on a regular basis to assure the comparability of the measurements across surveys. All volumes were corrected to body temperature and pressure saturated with water vapor (BTPS). Three measures of pulmonary function were obtained from the spirograms: FVC, forced expiratory volume in one second (FEV_1), and forced expiratory flow between 25 and 75% of the vital capacity (FEF_{25-75}). FEV_1 measurements with appropriate back extrapolation were accepted from tracings from which FVC measurements could not be made (12). In the present analysis, the maximum recorded FEV_1, FEF_{25-75}, and FVC (13) (not necessarily from the same tracing) were used. Each subject's standing height (ht) without shoes was measured to the nearest 0.5 inch and converted to centimeters for this analysis. Mean function values were converted into percentage of predicted values using the nomograms of Dickman and colleagues (15).

Methods of Data Analysis

For preliminary percentage of predicted analyses (table 2), pulmonary function was compared by two-sample t tests with two-sided p values. Two-sample t tests with two-sided p values were used to compare, by sex, asthmatic subjects with respect to age of onset of asthma, total number of years of active asthma, total number of years of medication for asthma, number of years smoking, and total number of cigarettes smoked. Fisher's exact test with two-sided p values calculated according to the "horizontal line method" (16) was used to compare the numbers of male and female asthmatic subjects reporting hospitalization for asthma and illness before age 2, and by sex the numbers of asthmatic and nonasthmatic personal ever-smokers.

A first-order autoregressive model (8, 17) was used to estimate the effect of smoking and asthma history on lung function separately for males and females. This method accommodates the longitudinal nature of the data and is particularly easy to implement and interpret because it is implemented using a modification of linear regression, a technique included in most statistical software packages. The usual linear regression model is not appropriate for longitudinal data because the repeated observations on individuals are not independent.

To implement the method the natural logarithm of lung function at each time period for each child was used as the dependent variable in a linear regression that included lung function in the previous time period as an independent variable along with sex, age, height, change in height, maternal smoking, personal smoking, active asthma, and inactive asthma. Adjustment for the residual correlation between the lung functions of siblings in the same study year was accomplished by including a random effect for each family study-year combination (18). The differential effects of sex were examined by including interaction terms between sex and the independent variables. Sex, the asthma variables, and the sex-asthma interactions were kept in all models, but other sex interaction terms were retained only if they were statistically significant. Model adequacy and validity were checked by examining residual plots and autocorrelation functions (19).

Finally, a second-order autoregressive model was fit to the data, and these results compared to the results of the first-order autoregressive model. This model predicts the current pulmonary function as a function of the two previous years values. Because this model reduces the effective sample size by 25% and thus adversely effects study power and because, in our judgment, the results were essentially the same as the first-order models, only the first-order results are presented in table 4. We note that the second-order term was significant for each of the three lung function measures, however, thus indicating the possibility of an improved fit using second-order models. The results of the first- and second-order models are contrasted in table 5.

The coefficient for the current asthma variable can be interpreted as the increase or decrease in the logarithm of lung function in any given time period associated with the presence of current asthma, holding constant all other terms in the model, including lung function in the previous period. A method for propagating the increase or decrease over several periods is given by Rosner and coworkers (17) and has been modified slightly to produce the projections shown in figures 1 and 2. Because our regression model used the logarithm of lung function, we obtained the percentage effects shown in table 4 by exponentiating the appropriate regression

Effects of Asthma on Pulmonary Function in Children

A Longitudinal Population-based Study[1-3]

SCOTT T. WEISS, TOR D. TOSTESON, MARK R. SEGAL, IRA B. TAGER, SUSAN REDLINE, and FRANK E. SPEIZER

SUMMARY Data from a longitudinal study of childhood factors influencing the development of chronic obstructive lung disease were used to assess the effects of asthma on lung function development in male and female children. A population-based cohort of 602 white children, initially aged 5 to 9 yr, was observed prospectively for 13 yr. Spirometry was performed and a standardized respiratory and illness questionnaire was administered by trained interviewers on a yearly basis. Forced vital capacity (FVC), forced expiratory volume in one second (FEV_1), and forced expiratory flow between 25 and 75% of vital capacity (FEF_{25-75}) were used as measures of lung function. The total number of children reporting asthma over the course of the study was 67. Male asthmatic subjects (n = 42) had larger average percentage of predicted FVC than nonasthmatic males (n = 277). Female asthmatic subjects (n = 23) had a lower average percentage of predicted FEV_1 than nonasthmatic females (n = 260). In a multivariate analysis of the individual lung function measures, adjusting for previous level of pulmonary function, age, height, change in height, and personal and maternal smoking, males reporting active asthma had a significantly larger FVC than males with no history of asthma. In contrast, females with active asthma had a significantly smaller FEV_1 than females with no history of asthma. Both males and females with active asthma had decreased FEF_{25-75}. From our analysis, we would predict that a female who develops asthma at age 7 would experience a 5% reduction in FEV_1 by age 10 and a 7% deficit by age 15. In our sample, asthmatic females had a greater risk of hospitalization for asthma than male asthmatic subjects (4 of 23, 6%, versus 1 of 42, 2%; p = 0.049). These results demonstrate apparent sex differences in the relationship between asthma and lung function development, with males more likely to have asthma but females experiencing a greater deficit in pulmonary function. AM REV RESPIR DIS 1992; 145:58-64

Introduction

To date only a few investigations (1-5) have explored the effect of a history of asthma on lung function in children. No study has characterized subjects at more than two points in time, and male-female differences have not been clearly explored. In this paper, we report on the analysis of data for a cohort of 602 children examined annually over a 13-yr period. During the course of the study, sufficient numbers of both male and female asthmatic children were identified to permit the characterization of male-female differences in the effect of asthma on pulmonary function.

Typically, asthmatic children have pulmonary function within the normal range in adolescence or young adulthood, with asthmatic symptoms tending to remit in a variable percentage as children grow (1-5). The presence of active symptoms is associated with lower levels of pulmonary function (1-4).

Cigarette smoking, direct (6) and passive (7, 8), has been shown to impair the growth of lung function in children and adolescents, and cross-sectional investigations have identified maternal smoking as a factor influencing airways responsiveness and level of lung function among asthmatic subjects (9, 10). Thus any analysis of lung function development among asthmatic subjects must take account of the effects of personal and maternal smoking. In our cohort, smoking history and other potential confounding factors have been documented through the use of a detailed annual questionnaire, and as a result, we are able to make appropriate adjustments to our estimate of the effect of asthma on pulmonary function.

Methods

Population Selection and Screening

Details of the sample selection and screening have previously been reported (7, 11). Briefly, a 34% random sample was selected from all children aged 5 to 9 yr who enrolled in September 1974 in the public and parochial schools of East Boston, Massachusetts. East Boston is a small, geographically distinct, ethnically and socioeconomically homogeneous area of the city of Boston. All the children in our study are white and predominantly Italian-American.

These randomly selected 5 to 9 yr olds were considered the index children. Trained interviewers visited the households of the index children and enumerated all residents between January and June 1975. The residents of these households, including the index children, constituted the initial study population. Initial examination of the subjects was conducted between January and June 1975. Index subjects then were visited in their homes during the school year (September to June) for a total of 13 annual follow-up examinations. Other family members were visited in their homes only for follow-up examinations 3 through 13. Follow-up interviews were conducted whenever possible within 4 calendar weeks of the date of the previous year's interview, usually between 2:00 and 8:00 p.m. All follow-up examinations were performed by one of two original interviewers.

Respiratory Symptoms and Definition of Asthma

Standardized questionnaires were used to obtain a history of respiratory symptoms and illnesses, as well as smoking history and demographic data. At the initial examination and the first two follow-up examinations, sepa-

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tion requires prospectively collected data from birth to age 5 yr, a time period that antedates the age of entry to this investigation. Our analysis leaves unanswered the mechanism by which asthma exerts these effects. It is hoped that ongoing longitudinal studies will address these issues more completely.

It is important to consider the impact of treatment on our results. On average, males and females did not differ in their duration of asthma treatment (table 3) but the duration of treatment was substantially less than the duration of asthma symptoms (table 3). When treatment was included in the regression model, it was not a significant predictor for any of the indices of pulmonary function and asthma remained significant (results not shown). Nevertheless, these data do not directly address the important question of whether aggressive, sustained treatment of asthma in childhood can influence the observed effects of asthma on lung function in children.

In summary, this longitudinal analysis demonstrates male-female differences in the influence of asthma on change in lung function as represented by FVC, FEV_1, and FEF_{25-75}. Asthma was more prevalent in males but more severe as measured by level of function and hospitalization in females in this cohort. Even in mild asthma with initially normal pulmonary function, the growth patterns lie outside the 95% confidence limits of nonasthmatic children. Whether the effects of asthma on change in pulmonary function observed in this study are linked to the airway abnormalities or are linked in some more fundamental way to hormonal, nutritional, or other influences on lung growth and maturation is unknown and unanswerable from the present analysis. Further research is necessary to determine the reasons for these differences and their implications for adult lung disease.

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